Neuroendocrine Tumor of the Bladder

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Small cell carcinoma (SCC) of the bladder is a rare and aggressive tumor associated with a poor prognosis. It often presents at a later stage than urothelial carcinoma of the bladder, and comprises less than 1% of bladder malignancies. A number of treatment algorithms have been used to treat bladder SCC, including cystectomy, partial cystectomy, radiotherapy, chemoradiotherapy, chemotherapy alone, and neoadjuvant/adjuvant chemotherapy. Presented is a case of SCC of the bladder, and the epidemiology, prognosis, and current treatment algorithms for patients with bladder SCC are reviewed.
[Rev Urol. *2010;12(4):e197-e201 doi: 10.3909/riu0492*]

Key Words: Bladder cancer • Neuroendocrine tumors • Small cell carcinoma

In 2008, the incidence of bladder cancer was 68,810 cases per year in the United States.[1] It is 3 times more common in men than in women. In men, it is the fourth most common malignancy after prostate, lung, and colorectal cancers.[2] In women, bladder cancer is the ninth most common cancer. More than 90% of bladder cancers are urothelial carcinomas. The 2 most common nonurothelial epithelial malignancies of the bladder are squamous cell carcinoma and adenocarcinoma. Neuroendocrine tumors are less common than the above histologic variants in the genitourinary system, and are classified into 2 subtypes: carcinoid tumor and neuroendocrine carcinoma. Neuroendocrine carcinoma is further subdivided into small cell carcinoma (SCC) and large cell neuroendocrine carcinoma, the latter of which is exceedingly rare in the bladder.[3] SCC of the bladder comprises only 0.5% to 1.0% of primary bladder malignancies. It most commonly presents in

the seventh decade, with a male: female ratio of 2:1 to 5:1. Unlike lung SCC, bladder SCC rarely is associated with paraneoplastic syndromes. Pure SCC of the bladder is infrequent and is usually mixed with another histologic subtype (most commonly urothelial carcinoma).[3] SCC of the bladder usually behaves more aggressively than urothelial carcinoma and carries a worse prognosis, often because patients present at a later stage as compared with urothelial carcinoma.[4]

The bladder is the most common site for genitourinary extrapulmonary SCC.[5] We describe a case of poorly differentiated neuroendocrine carcinoma of the urinary bladder presenting with gross hematuria in an 83-year-old woman.

Case Presentation

RB is an 83-year-old woman who was admitted to the medicine service at our institution with documented urinary tract infection (UTI) and history of gross hematuria. Past medical history is significant for endometrial carcinoma, status post–total abdominal hysterectomy/bilateral salpingoophorectomy in the 1970s, chronic lymphedema, chronic kidney disease (Cr 1.5-1.7), hypertension, and mild dementia. She initially presented to her nephrologist with a chief complaint of gross hematuria. A renal ultrasound was obtained at an outside facility and revealed multiple liver masses. Abdominal ultrasound at our institution corroborated these findings, showing several hyperechoic hepatic masses, the largest in the left lateral hepatic lobe, measuring 3.4 × 3.8 × 3.6 cm. Fine needle aspiration (FNA) of this liver mass showed poorly differentiated carcinoma with neuroendocrine features, thought to be indolent, and therefore managed with close follow-up only. The patient returned to her primary medical doctor 3 months after liver FNA again with gross hematuria. Magnetic resonance imaging (MRI) of the abdomen and pelvis with gadolinium revealed a bladder mass measuring 7.5 × 8.3 × 8.9 cm, with extravesical extension, multiple liver metastases (at least 12), occupying approximately 50% of the liver volume, with peripheral T2 enhancement, and presacral lymphadenopathy (Figure 1). She was readmitted for further management. Cystoscopy showed a bullous, fluffy, white tumor occupying the bladder dome, posterior wall, left lateral wall, and bladder outlet. She underwent transurethral resection of this bladder mass for pathologic diagnosis.

Transurethral resection bladder tumor (TURBT) specimen showed poorly differentiated carcinoma, involving detrusor muscle, with focal neuroendocrine differentiation. The tumor was positive for AE1/AE3 and synaptophysin, negative for CK903, p63, thrombomodulin, leukocyte common antigen (LCA), and S100. Immunostain for chromogranin was equivocal (Figure 2). Tumor cell clusters from the liver FNA cell appeared cytomorphologically similar to the tumor in the bladder, both with focal neuroendocrine differentiation based on immunohistochemistry. Given her metastatic disease, she was referred to medical oncology for systemic chemotherapy.

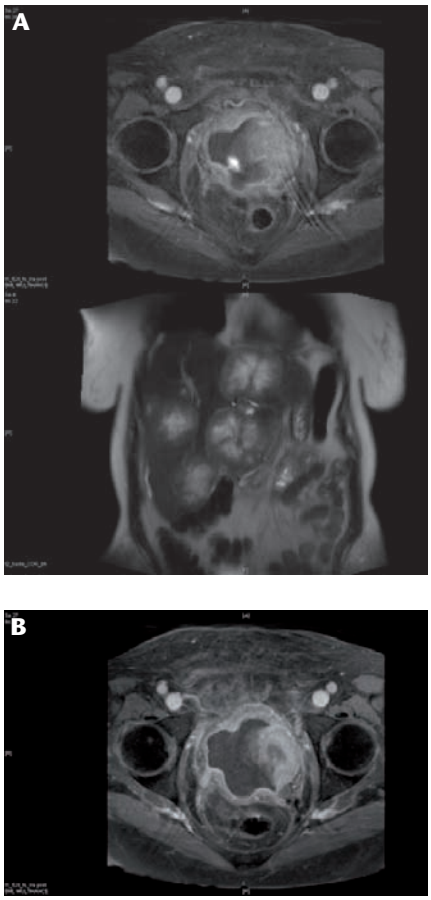

Figure 1. (A) *Liver metastases and* **(B)** *bladder mass on T2-weighted magnetic resonance imaging.*

Discussion

As with urothelial carcinoma, patients with SCC can present with dysuria, obstructive voiding symptoms, weight loss, abdominal pain, ureteral obstruction, and/or recurrent UTIs.[4] In both urothelial carcinoma and SCC of the bladder, the most common presentation is painless hematuria (67%-100% in bladder SCC).[6] Cigarette smoking is a risk factor for SCC of the bladder with 50% to 70% of patients reporting a smoking history.[6] Bladder SCC more often presents at a later stage than urothelial carcinoma. As such, worse outcomes are associated with SCC of the bladder. Bladder SCC presents as stage I in 0% to 5% of patients, stage II in 27% to 44% of patients, stage III in 24% to 30% of patients, and stage IV in 27% to 43% of patients.[6] Median survival of all those with

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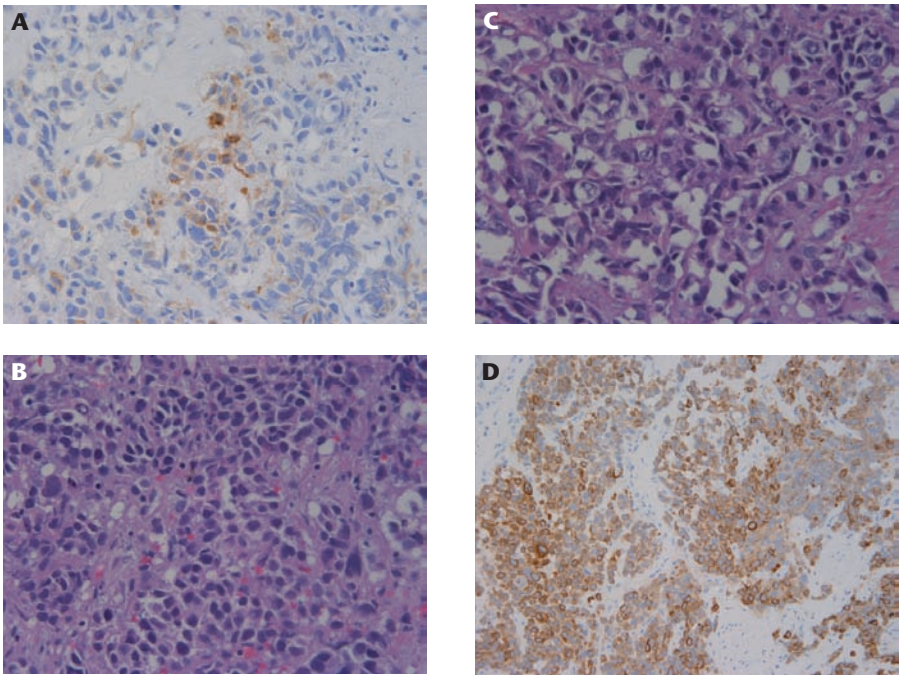

Figure 2. *Pathologic specimen from transurethral resection. On hematoxylin and eosin stains, the tumor shows* (A) *sheets of poorly differentiated cells (×200) with* (B) *high nuclear and cytoplasm ratio (×400). However, the tumor cells have more abundant cytoplasm than the classic small cell carcinoma (SCC). Immunohistochemical stains show that the tumor is* (C) *positive for cytokeratin (AE1/3) and* (D) *focally positive for synaptophysin.*

bladder SCC is 20 to 23 months.[4] Prognosis is dependent on performance status and extent of disease at diagnosis, whereas overexpression of p53, patient age, gender, and presenting symptoms do not appear to correlate with prognosis.[6] In addition, it has been found that pure SCC tends to have a poorer outcome than mixed SCC of the bladder.[7]

At cystoscopy, SCC cannot be differentiated from urothelial carcinoma by its morphologic appearance.[5] Diagnosis is confirmed with transurethral resection for tissue sampling. Histologically, the diagnosis is supported by positive immunostaining for keratin Cam 5.2, synaptophysin, and chromogranin. Chromogranin is positive in one-half of the cases of SCC but only 5% of urothelial carcinoma.[5] Also, 40% of bladder SCCs express thyroid transcription factor.[4] Treatment is dependent on tumor stage at presentation and patient performance status. The low incidence of SCC of the urinary bladder has made it difficult to establish definitive treatment algorithms. Cystectomy, partial cystectomy, transurethral resection, and radiotherapy have all been used to treat local disease.[6] Neoadjuvant and adjuvant chemotherapy have been used with these modalities as well as chemotherapy alone.[6] TURBT alone is usually not curative and is associated with survival rates of 3 to 6 months.[6] TURBT alone is reserved for patients not able to tolerate more aggressive therapies or for palliation of symptoms. Individuals who undergo TURBT with radiotherapy have been reported to have a median survival of 5 to 6.5 months in small, retrospective case series.[6] Surgery alone (cystectomy or partial cystectomy) is reserved for early stage bladder SCC (stage I and II).[6] Long-term survival has been reported for stage II disease. Choong and colleagues[8] reported cure in 6 of 8 (75%) patients with stage II SCC treated with radical cystectomy alone in a retrospective review of 44 patients from 1975 to 2003.

Neoadjuvant or adjuvant cisplatinum-based chemotherapy has been used with radical cystectomy to potentially improve long-term survival in bladder SCC.[6] In a retrospective review of 25 patients with neuroendocrine tumor of the bladder, Quek and associates[9] reported significant improvement in recurrence-free and overall survival (OS) in those receiving neoadjuvant or adjuvant chemotherapy with radical cystectomy as compared with radical cystectomy alone. Siefker-Radtke and colleagues[10] reported similar results with regard to neoadjuvant chemotherapy but not with adjuvant chemotherapy. In a retrospective review of 88 patients, individuals treated with neoadjuvant chemotherapy had 78% disease-specific 5-year survival rates as compared with only 36% among those treated with cystectomy alone. In contrast, there was no survival advantage conferred with adjuvant chemotherapy compared with cystectomy alone. Neoadjuvant therapy may be advantageous in this patient population compared with adjuvant therapy because a large number of patients with SCC exhibit rapid growth rates making complete resection difficult or impossible secondary to rapidly progressive local disease.[10] Other studies, however, have shown no survival benefit between cystectomy and multimodal therapy. For example, Cheng and colleagues[11] reported no survival benefit in 64 cases of SCC in those undergoing cystectomy alone compared with multimodal treatment. Choong and coauthors[8] recommend no adjuvant chemotherapy for stage I and II disease after reporting a 75% cure rate with radical cystectomy alone for stage II disease.

Based on treatment algorithms for SCC of the lung, some clinicians have developed combined chemotherapy/radiotherapy/TURBT regimens as a bladder-sparing alternative to cystectomy.[6] It is difficult to judge the most optimum local therapy, as there are no direct comparisons between radiotherapy and cystectomy alone.[5] Lohrisch and colleagues[12] retrospectively reviewed 14 cases of bladder SCC treated with combined chemoradiation in patients with primarily stage III or less disease. They observed a 70% 2-year survival and 44% 5-year OS in these individuals. Cisplatin-based chemotherapy was the primary chemotherapeutic regimen used.[12] Bex and colleagues[13] also reported success with a bladder-sparing approach, with 64.7% (n = 11) of patients exhibiting a clinical complete response, 8 with chemoradiotherapy and 3 with transurethral resection (TUR) and radiotherapy. Indeed, platinum-based chemotherapy is the mainstay of treatment of recurrent and metastatic disease.[7,14] Mackey and associates[15] retrospectively reviewed the records of 180 patients with genitourinary SCC. Patient age, sex, primary site, histologic features, tumor size, stage, locoregional therapy, systemic chemotherapy, and hormonal therapy were analyzed for association with survival. For bladder SCC, only cisplatin-based chemotherapy predicted survival on multivariate analysis.[15] One of the drawbacks of chemoradiotherapy is the occurrence of urothelial carcinoma of the bladder, which has been shown to occur in 20% to 60% of patients.[12,16]

Data for bladder SCC treatment regimens are available almost exclusively from retrospective reviews due to low disease incidence. As such, it is difficult to establish authoritative treatment guidelines. Most patients present at late stages and therefore need multimodal therapy. A number of studies have shown survival benefit in low-stage disease when neoadjuvant therapy is used prior to cystectomy. However, others contend that no survival benefit is gained by adding neoadjuvant or adjuvant therapy to cystectomy alone for low-stage disease. Reasonable results have been demonstrated using chemoradiotherapy bladder-sparing protocols, which may be an attractive option in treating poor surgical candidates. However, one pitfall of bladder-sparing protocols is the high occurrence of residual or recurrent carcinoma in the preserved bladder.

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Conclusions

Bladder SCC usually presents at a later stage than urothelial carcinoma and therefore confers a worse prognosis. Multiple treatment algorithms have been used to treat local and metastatic disease, including cystectomy, partial cystectomy, radiation therapy, and neoadjuvant/adjuvant chemotherapy as well as chemotherapy alone. Low disease incidence makes it difficult to exclusively advocate for one treatment algorithm. Prospective studies need to be done to elucidate the most effective treatment by stage for bladder SCC. ■

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Main Points

- Neuroendocrine tumors are classified into 2 subtypes: carcinoid tumor and neuroendocrine carcinoma. Neuroendocrine carcinoma is further subdivided into small cell carcinoma (SCC) and large cell neuroendocrine carcinoma, the latter of which is exceedingly rare in the bladder.
- As with urothelial carcinoma, patients with SCC can present with dysuria, obstructive voiding symptoms, weight loss, abdominal pain, ureteral obstruction, and/or recurrent urinary tract infections.
- Diagnosis of bladder SCC is confirmed with transurethral resection for tissue sampling, and is supported histologically by positive immunostaining for keratin Cam 5.2, synaptophysin, and chromogranin. Chromogranin is positive in one-half of the cases of SCC but only 5% of urothelial carcinoma.
- Multiple treatment algorithms for SCC of the bladder have been used to treat local and metastatic disease, including cystectomy, partial cystectomy, radiation therapy, and neoadjuvant/adjuvant chemotherapy as well as chemotherapy alone. Low disease incidence makes it difficult to exclusively advocate for one treatment algorithm.

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